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Applicant	:	AGUET)	Group Art Unit: 1642
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Appl. No.	:	09/442,898)	
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Filed	:	November 18, 1999)	
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For	:	USES FOR EPH RECEPTOR)	
		ANTAGONISTS AND)	
		AGONISTS)	
)	
Examiner	:	NICKOL, G.)	

RESPONSE TO FINAL OFFICE ACTION

United States Patent and Trademark Office
P.O. Box 2327
Arlington, VA 22202

04/01/2002 SSESHE1 00000006 09442898

01 FC:116
02 FC:119400.00 OP
320.00 OP

Dear Sir:

This is in response to the final Office Action mailed on October 23, 2001 in connection with the above-identified patent application. A request for a two months extension of time accompanies the present response, setting the time for response to March 23, 2002. Also enclosed is a Notice of Appeal against the final rejection of claims 1-2, 4-6, and 23.

Claims 1-2, 4-6, and 23 (all claims pending in this application) have been rejected under 35 U.S.C. § 103 as allegedly obvious over Caras (WO 96/13518) in view of Wang *et al.* (Cell, Vol. 93, pages 741-753, 1998). In addressing Applicant's arguments in response to a similar rejection in Paper No. 8, the Examiner noted that: (1) Wang *et al.* "clearly demonstrated the role of an EphB receptor, such as EphB4, in angiogenesis; (2) Applicant addressed the references individually, instead of analyzing their combination; and (3) the "test of obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art."

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The Legal Standard

When an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. The suggestion to combine may be found in explicit or implicit teachings within the references themselves, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved. In other words, when determining the patentability of a claimed invention over the combination of references, the first question is whether there is something in the prior art as a whole to suggest the desirability of making the combination. *WMS Gaming, Inc. v. International Game Technology*, 184 F.3d 1339, 1355 (Fed. Cir. 1999); *B.F. Goodrich Co. v. Aircraft Braking Systems*, 72 F.3d 1577, 1582 (Fed.Cir.1996); *In re Dance*, 160 F.3d 1339, 1342 (Fed. Cir. 1998); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed.Cir.1992). Accordingly, when a claimed invention is rejected as obvious over a combination of prior art references, a proper analysis requires the consideration of (1) whether the references themselves or the prior art as a whole had any suggestion of combining the teaching of the references relied upon in the rejection; (2) whether the combination would have suggested to those of ordinary skill in the art that they should make the claimed invention; and (3) whether the combination would also have revealed that those of ordinary skill in the pertinent art would have a reasonable expectation of success. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d (BNA) 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. Obviousness cannot be established by hindsight combination to produce the claimed invention. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed.Cir.1991). It is the prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination.

The Combination of Caras and Wang et al. is Legally Improper

The family of Eph receptors is one of the largest families of protein tyrosine kinases. To date, at least fourteen distinct receptors and eight ligands of this family have been identified in mammals, and implicated in a variety of cell-cell interactions involved in nervous system patterning, including axon guidance, and angiogenesis. The Eph receptors are divided into two groups, based on the relatedness of their extracellular domain sequences, and their ability to bind

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preferentially to the ephrin-A or ephrin-B proteins. The group that includes homologous receptors interacting preferentially with ephrin-A proteins is called EphA, while the group that includes homologous receptors interacting preferentially with ephrin-B proteins is called EphB.

The invention claimed in the present application concerns a method of inhibiting angiogenesis by administering an Eph receptor antagonist, which binds an EphB receptor, such as EphB4.

Caras concerns the AL-1 neurotrophic factor, also known as ephrin-A5, which binds an EphA receptor. Caras also discloses that AL-1 (ephrin-A5) antagonists are useful in treating various neuronal disorders and disorders or conditions associated with angiogenesis.

Wang *et al.* teaches that ephrin-B2 knockout mice display certain defects in angiogenesis by both arteries and veins, and suggest that reciprocal signaling between ephrin-B2 expressed on arterial cells, and EphB4 expressed on venous cells may play an important role in remodeling the capillary network during angiogenesis.

Receptors of the EphA and EphB families differ significantly in their sequences, in their ligand preferences, and in their physiological roles. In view of the distinctness of the EphA and EphB receptors and their ligands, a person of ordinary skill in the art would find findings based on the study of an EphA receptor or its ligand not particularly helpful when addressing the biological role of an EphB receptor or its ligand. Therefore, despite the teaching that both ephrin-A5 and ephrin-B2 appear to be involved in some aspects of angiogenesis, a skilled artisan would have had no motivation at the time when the present invention was made to combine the teachings of Caras and Wang *et al.*

The Combination of Caras and Wang et al. Would Not Have Suggested to Those of Ordinary Skill in the Art to Make the Claimed Invention

The combination of Caras and Wang *et al.*, even if it were legally proper, would not have suggested to one of ordinary skill in the art to make the invention claimed in the present application.

There is nothing in the combination of Caras and Wang *et al.* that would suggest to one skilled in the art that the interaction of ephrin-A5 with its EphA receptor would share any similarity with the interaction of ephrin-B2 and its EphB4 receptor. Furthermore, Caras or Wang *et al.*, or their combination, teaches nothing about the ability of Eph receptor antagonists (either

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A or B) to inhibit angiogenesis. Indeed, Wang *et al.* describes a rather complex relationship between ephrin-B2 and Eph-B4, suggesting that Ang-1 "could be [additionally] necessary for the expression or function of the ephrin-B2-Eph-B4 ligand-receptor pair" (page 751, second column). Based on this teaching, and also in view of the statement that "[t]argeted disruption of Eph-B4 should directly address the question of whether this receptor is required for signaling from veins to arteries" (page 750, sentence bridging columns 1 and 2), without the benefit of the present invention, one skilled in the art would have had no reasonable expectation of successfully inhibiting angiogenesis via EphB receptor antagonists. It is only the present disclosure that creates a reasonable expectation of success, which is, of course, not available for obviousness determination.

In conclusion, Caras and Wang *et al.* were not properly combined, and even if their combination had been proper, their combined disclosures do not create a reasonable expectation of the successful performance of the invention disclosed and claimed in the present application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the pending rejection.


All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 25, 2002

By: 

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